

(FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS,
MEDICONF'

ENTERED AT 16:56:13 ON 06 JAN 2000)

DEL HIS

L1 1393 S DAF-18 OR PTEN
L2 37 S L1 AND ELEGANS
L3 11 DUP REM L2 (26 DUPLICATES REMOVED)
L4 11 SORT L3 PY
L5 51 S L1 AND MODULAT?
L6 15 DUP REM L5 (36 DUPLICATES REMOVED)
L7 15 SORT L6 PY

(FILE 'HOME' ENTERED AT 16:45:07 ON 06 JAN 2000)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 16:45:12 ON 06 JAN 2000

L1 1393 S DAF-18 OR PTEN
L2 0 S L1 AND OBESITY
L3 7 S L1 AND TRANSGENIC
L4 3 DUP REM L3 (4 DUPLICATES REMOVED)
L5 3 SORT L4 PY
L6 37 S L1 AND ELEGANS
L7 11 DUP REM L6 (26 DUPLICATES REMOVED)
L8 11 SORT L7 PY

=> d ti so au ab pi 18 1-11

L8 ANSWER 1 OF 11 MEDLINE
TI Genetic analysis of chemosensory control of dauer formation in
Caenorhabditis **elegans**.
SO GENETICS, (1992 Jan) 130 (1) 105-23.
Journal code: FNH. ISSN: 0016-6731.
AU Vowels J J; Thomas J H
AB Dauer larva formation in Caenorhabditis **elegans** is controlled by
chemosensory cells that respond to environmental cues. Genetic
interactions among mutations in 23 genes that affect dauer larva
formation
were investigated. Mutations in seven genes that cause constitutive dauer
formation, and mutations in 16 genes that either block dauer formation or
result in the formation of abnormal dauers, were analyzed. Double mutants
between dauer-constitutive and dauer-defective mutations were constructed
and characterized for their capacity to form dauer larvae. Many of the
genes could be interpreted to lie in a simple linear epistasis pathway.
Three genes, daf-16, **daf-18** and daf-20, may affect
downstream steps in a branched part of the pathway. Three other genes,
daf-2, daf-3 and daf-5, displayed partial or complex epistasis
interactions that were difficult to interpret as part of a simple linear
pathway. Dauer-defective mutations in nine genes cause structurally
defective chemosensory cilia, thereby blocking chemosensation. Mutations
in all nine of these genes appear to fall at a single step in the
epistasis pathway. Dauer-constitutive mutations in one gene, daf-11, were
strongly suppressed for dauer formation by mutations in the nine
cilium-structure genes. Mutations in the other six dauer-constitutive
genes caused dauer formation despite the absence of functional
chemosensory endings. These results suggest that daf-11 is directly
involved in chemosensory transduction essential for dauer formation,
while
the other Daf-c genes play roles downstream of the chemosensory step.

L8 ANSWER 2 OF 11 MEDLINE
TI The age-1 and daf-2 genes function in a common pathway to control the
lifespan of Caenorhabditis **elegans**.
SO GENETICS, (1995 Dec) 141 (4) 1399-406.
Journal code: FNH. ISSN: 0016-6731.
AU Dorman J B; Albinder B; Shroyer T; Kenyon C
AB Recessive mutations in two genes, daf-2 and age-1, extend the lifespan of
Caenorhabditis **elegans** significantly. The daf-2 gene also
regulates formation of an alternative developmental state called the
dauer. Here we asked whether these two genes function in the same or

and different lifespan pathways. We found that the longevity of both age-1 daf-2 mutants requires the activities of the same two genes, daf-16 and **daf-18**. In addition, the daf-2(e1370); age-1(hx546) double mutant did not live significantly longer than the daf-2 single mutant. We also found that, like daf-2 mutations, the age-1(hx546) mutation affects certain aspects of dauer formation. These findings suggest that age-1 and daf-2 mutations do act in the same lifespan pathway
and extend lifespan by triggering similar if not identical processes.

L8 ANSWER 3 OF 11 MEDLINE
TI Genes that regulate both development and longevity in *Caenorhabditis elegans*.
SO GENETICS, (1995 Apr) 139 (4) 1567-83.
Journal code: FNH. ISSN: 0016-6731.
AU Larsen P L; Albert P S; Riddle D L
AB The nematode *Caenorhabditis elegans* responds to conditions of overcrowding and limited food by arresting development as a dauer larva. Genetic analysis of mutations that alter dauer larva formation (daf mutations) is presented along with an updated genetic pathway for dauer vs. nondauer development. Mutations in the daf-2 and daf-23 genes double adult life span, whereas mutations in four other dauer-constitutive genes positioned in a separate branch of this pathway (daf-1, daf-4, daf-7 and daf-8) do not. The increased life spans are suppressed completely by a daf-16 mutation and partially in a daf-2; **daf-18** double mutant. A genetic pathway for determination of adult life span is presented based on the same strains and growth conditions used to characterize Daf phenotypes. Both dauer larva formation and adult life span are affected in daf-2; daf-12 double mutants in an allele-specific manner. Mutations in daf-12 do not extend adult life span, but certain combinations of daf-2 and daf-12 mutant alleles nearly quadruple it. This synergistic effect, which does not equivalently extend the fertile period,
is the largest genetic extension of life span yet observed in a metazoan.

L8 ANSWER 4 OF 11 MEDLINE
TI The *C. elegans* PTEN homolog, **DAF-18**, acts in the insulin receptor-like metabolic signaling pathway.
SO MOLECULAR CELL, (1998 Dec) 2 (6) 887-93.
Journal code: C5E. ISSN: 1097-2765.
AU Ogg S; Ruvkun G
AB An insulin-like signaling pathway, from the DAF-2 receptor, the AGE-1 phosphoinositide 3-kinase, and the AKT-1/AKT-2 serine/threonine kinases to the DAF-16 Fork head transcription factor, regulates the metabolism, development, and life span of *Caenorhabditis elegans*. Inhibition of **daf-18** gene activity bypasses the normal requirement for AGE-1 and partially bypasses the need for DAF-2 signaling.

The suppression of age-1 mutations by a **daf-18** mutation depends on AKT-1/AKT-2 signaling, showing that **DAF-18** acts between AGE-1 and the AKT input to DAF-16 transcriptional regulation. **daf-18** encodes a homolog of the human tumor suppressor **PTEN** (MMAC1/TEP1), which has 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate (PIP3). **DAF-18 PTEN** may normally limit AKT-1 and AKT-2 activation by decreasing PIP3 levels. The action of **daf-18** in this metabolic control pathway suggests that mammalian **PTEN** may modulate insulin signaling and may be variant in diabetic pedigrees.

L8 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2000 ACS
TI Evolutionary fates and origins of U12-type introns
SO Mol. Cell (1998), 2(6), 773-785

CODEN: MOCEFL; ISSN: 1097-2765

AU Burge, Christopher B.; Padgett, Richard A.; Sharp, Phillip A.

AB U2-type and U12-type introns are spliced by distinct spliceosomes in eukaryotic nuclei. A classification method was devised to distinguish these two types of introns based on splice site sequence properties and was used to identify 56 different genes contg. U12-type introns in available genomic sequences. U12-type introns occur with consistently low

frequency in diverse eukaryotic taxa but have almost certainly been lost from *C. elegans*. Comparisons with available homologous sequences demonstrate subtype switching of U12 introns between termini of AT-AC and GT-AG as well as conversion of introns from U12-type to U2-type and provide evidence for a fission/fusion model in which the two splicing systems evolved in sep. lineages that were fused in a eukaryotic progenitor.

L8 ANSWER 6 OF 11 MEDLINE

TI The **PTEN** tumor suppressor homolog in *Caenorhabditis elegans* regulates longevity and dauer formation in an insulin receptor-like signaling pathway.

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jun 22) 96 (13) 7427-32.

Journal code: PV3. ISSN: 0027-8424.

AU Mihaylova V T; Borland C Z; Manjarrez L; Stern M J; Sun H

AB Inactivation of the tumor suppressor **PTEN** gene is found in a variety of human cancers and in cancer predisposition syndromes.

Recently,

PTEN protein has been shown to possess phosphatase activity on phosphatidylinositol 3,4,5-trisphosphate, a product of phosphatidylinositol 3-kinase. We have identified a homolog of **PTEN** in *Caenorhabditis elegans* and have found that it corresponds to the **daf-18** gene, which had been defined by a single, phenotypically weak allele, **daf-18** (e1375). By analyzing an allele, **daf-18**(nr2037), which bears a deletion of the catalytic portion of CePTEN/DAF-18, we have shown that mutation in **daf-18** can completely suppress the dauer-constitutive phenotype caused by inactivation of **daf-2** or **age-1**, which encode an insulin receptor-like molecule and the catalytic subunit of phosphatidylinositol 3-kinase, respectively. In addition, **daf-18**(nr2037) dramatically shortens lifespan, both in a wild-type background and in a **daf-2** mutant background that normally prolongs lifespan. The lifespan in a **daf-18**(nr2037) mutant can be restored to essentially that of wild type when combined with a **daf-2** mutation. Our studies provide genetic evidence that, in *C. elegans*, the **PTEN** homolog **DAF-18** functions as a negative regulator of the **DAF-2** and **AGE-1** signaling pathway, consistent with the notion that **DAF-18** acts a phosphatidylinositol 3,4,5-trisphosphate phosphatase in vivo. Furthermore, our studies have uncovered a longevity-promoting activity of the **PTEN** homolog in *C. elegans*.

L8 ANSWER 7 OF 11 MEDLINE

TI Regulation of dauer larva development in *Caenorhabditis elegans* by **daf-18**, a homologue of the tumour suppressor **PTEN**.

SO CURRENT BIOLOGY, (1999 Mar 25) 9 (6) 329-32.

Journal code: B44. ISSN: 0960-9822.

AU Rouault J P; Kuwabara P E; Sinilnikova O M; Duret L; Thierry-Mieg D; Billaud M

AB The tumour suppressor gene **PTEN** (also called MMAC1 or TEP1) is somatically mutated in a variety of cancer types [1] [2] [3] [4]. In addition, germline mutation of **PTEN** is responsible for two dominantly inherited, related cancer syndromes called Cowden disease and Bannayan-Ruvalcaba-Riley syndrome [4]. **PTEN** encodes a dual-specificity phosphatase that inhibits cell spreading and migration

partly by inhibiting integrin-mediated signalling [5] [6] [7]. Furthermore, **PTEN** regulates the levels of phosphatidylinositol 3,4,5-trisphosphate (PIP3) by specifically dephosphorylating position 3

on

the inositol ring [8]. We report here that the dauer formation gene **daf-18** is the *Caenorhabditis elegans* homologue of **PTEN**. **DAF-18** is a component of the insulin-like signalling pathway controlling entry into diapause and adult longevity that is regulated by the DAF-2 receptor tyrosine kinase and the AGE-1 PI 3-kinase [9]. Others have shown that mutation of **daf-18** suppresses the life extension and constitutive dauer formation associated with **daf-2** or **age-1** mutants. Similarly, we show that inactivation of **daf-18** by RNA-mediated interference mimics this suppression, and that a wild-type **daf-18** transgene rescues the dauer defect. These results indicate that **PTEN/daf-18** antagonizes the DAF-2-AGE-1 pathway, perhaps by catalyzing dephosphorylation of the PIP3 generated by AGE-1. These data further support the notion that mutations of **PTEN** contribute to the development of human neoplasia through an aberrant activation of the PI 3-kinase signalling cascade.

- L8 ANSWER 8 OF 11 MEDLINE
TI Regulation of the insulin-like developmental pathway of *Caenorhabditis elegans* by a homolog of the **PTEN** tumor suppressor gene.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 16) 96 (6) 2925-30.
Journal code: PV3. ISSN: 0027-8424.
AU Gil E B; Malone Link E; Liu L X; Johnson C D; Lees J A
AB The human **PTEN** tumor suppressor gene is mutated in a wide variety of sporadic tumors. To determine the function of **PTEN** in vivo we have studied a **PTEN** homolog in *Caenorhabditis elegans*. We have generated a strong loss-of-function allele of the **PTEN** homolog and shown that the deficient strain is unable to enter dauer diapause. An insulin-like phosphatidylinositol 3-OH kinase (PI3'K) signaling pathway regulates dauer-stage entry. Mutations in either the **daf-2** insulin receptor-like (IRL) gene or the **age-1** encoded PI3'K catalytic subunit homolog cause constitutive dauer formation and also affect the life span, brood size, and metabolism of nondauer animals. Strikingly, loss-of-function mutations in the **age-1** PI3'K and **daf-2** IRL genes are suppressed by loss-of-function mutations in the **PTEN** homolog. We establish that the **PTEN** homolog is encoded by **daf-18**, a previously uncloned gene that has been shown to interact genetically with the DAF-2 IRL AGE-1 PI3'K signaling pathway. This interaction provides clear genetic evidence that **PTEN** acts to antagonize PI3'K function in vivo. Given the conservation of the PI3'K signaling pathway between *C. elegans* and mammals, the analysis of **daf-18** **PTEN** mutant nematodes should shed light on the role of human **PTEN** in the etiology of metabolic disease, aging, and cancer.
- L8 ANSWER 9 OF 11 SCISEARCH COPYRIGHT 2000 ISI (R)
TI Modulation of cellular apoptotic potential: contributions to oncogenesis
SO ONCOGENE, (1 NOV 1999) Vol. 18, No. 45, Sp. iss. SI, pp. 6094-6103.
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.
ISSN: 0950-9232.
AU Stambolic V; Mak T W; Woodgett J R (Reprint)
AB The importance of apoptosis as a natural means to eliminate unwanted damaged cells has been realized over the past decade. Many components required to exercise programmed cell death have been identified and shown to pre-exist in most, if not all, cells. Such ubiquity requires that apoptosis be tightly controlled and suggests the propensity of cells to trigger the cellular death machinery can be regulated. Recently several

signaling pathways have been demonstrated to impact the apoptotic potential of cells, most notably the phosphatidylinositol 3' kinase (PI3'K) pathway. The 3' phosphorylated lipid products generated by this enzyme promote activation of a protein-serine kinase, PKB/AKT, which is necessary and sufficient to confer cell PI3'K-dependent survival signals. The relevance of this pathway to human cancer was revealed by the recent finding that the product of the PTEN tumor suppressor gene acts to antagonize PI3'K. This review focuses on the regulation and mechanisms by which PKB activation protects cells and the oncologic consequences of dysregulation of the pathway.

- L8 ANSWER 10 OF 11 SCISEARCH COPYRIGHT 2000 ISI (R)
TI Forkhead transcription factors: new insights into protein kinase B
(c-akt)
 signaling
SO JOURNAL OF MOLECULAR MEDICINE-JMM, (SEP 1999) Vol. 77, No. 9, pp.
656-665.
 Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
 ISSN: 0946-2716.
AU Kops G J P L; Burgering B M T (Reprint)
AB The proto-oncogene protein kinase B (PKB), also known as c-Akt, is a central player in a signaling pathway of which many components have been linked to tumorigenesis. Active forms of PKB as well as of its upstream activator phosphatidylinositol 3-kinase (PI3K) have been found to be responsible for the transforming activities of certain viruses, and the negative regulator of this pathway, PTEN, is a tumor suppressor. The identification of particular downstream targets of PKB has provided us with new insights into the possible mechanism of PI3K/PKB-mediated tumorigenicity. Recently a subfamily of Forkhead transcription factors was identified as additional targets for PI3K/PKB signaling. This review discusses the studies that have led to this conclusion and the possible implications of this finding for our understanding of how PI3K/PKB activity could lead to oncogenesis.
- L8 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2000 ACS
TI Mechanisms of life span determination in *Caenorhabditis elegans*
SO Neurobiol. Aging (1999), 20(5), 487-502
CODEN: NEAGDO; ISSN: 0197-4580
AU Vanfleteren, J. R.; Braeckman, B. P.
AB Mol. anal. of several gerontogenes of *Caenorhabditis elegans* has led to the discovery of at least two life span-controlling pathways. An insulin-like signaling cascade consisting of proteins encoded by the genes daf-2, age-1, akt-1, akt-2, daf-16 and **daf-18** regulates dauer diapause, reprodn., and longevity. This pathway regulates all three processes systemically. daf-12 interacts with it, affecting dauer diapause and longevity. Life span extension mediated by this pathway probably results from the activation of an enhanced life-maintenance program, which is normally operative during dauer diapause. A different mechanism is specified by the clock genes clk-1, clk-2, clk-3 and gro-1, which regulate metabolic activity and the pace of many temporal processes including longevity. There is some controversy as to whether the life span extension obsd. in these mutants requires the activity of daf-16. All known gerontogenes appear to confer resistance to environmental stress, usually multiple stress factors, including oxidative stress, high temp., and exposure to UV radiation. Caloric restriction extends longevity substantially, and may act by activating the enhanced life-maintenance program.

